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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/421,422	10/19/1999	PEHR B. HARBURY	STAN-390	4130
24353 7590 02/07/2008 BOZICEVIC, FIELD & FRANCIS LLP 1900 UNIVERSITY AVENUE SUITE 200 EAST PALO ALTO, CA 94303			EXAMINER LIU, SUE XU	
			ART UNIT 1639	PAPER NUMBER
			MAIL DATE 02/07/2008	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/421,422

Applicant(s)

HARBURY ET AL.

Examiner

Sue Liu

Art Unit

1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 November 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-10 and 15-30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3-10 and 15-30 is/are rejected.
- 7) ☒ Claim(s) 1 and 5 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Claim Status

1. Claims 2 and 11-14 have been cancelled.

Claims 17-30 have been added as filed on 11/19/07.

Claims 1, 3-10 and 15-30 are currently pending.

Claims 1, 3-10 and 15-30 are being examined in this application.

Election/Restrictions

2. Applicant's election of Group I invention (original claims 1-10) of a method of synthesizing a plurality of compounds, in the Reply, filed on 3/26/2001, is as previously acknowledged.

Priority

3. This application claims priority to U.S. Provisional Patent Application Nos. 60/104,744, filed 10/19/1998.
4. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/104,744, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The amended claims recite a method step of “removing said first immobilized sequence” before step (c) of the instant claim 1. The said provisional application does not provide support for the said step of “removing said first immobilized sequence” before the chemical reaction step. The instant claim 1 is also amended to recite “wherein each of the first and second variable hybridization sequences is different for each subset of nucleic acid tags” in step (b), which also does not appear to have specific support in the priority document.

Thus, claims 1 and 23 as well as their dependent claims do not obtain the priority date of the said provisional application.

Claim Rejections Withdrawn

5. In light of applicant's amendments to the claims and arguments, the following claim rejections are withdrawn:

A) Claims 1, 3-8, 10, 15 and 16 are rejected under **35 U.S.C. 102(b)** as being anticipated by Brenner (US 5,635,400; 6/3/1997).

B.) Claims 1, 3-8, 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Rosenthal et al (WO9321340; 10/28/1993).

C.) Claims 1, 3-10, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenthal et al (WO9321340; 10/28/1993), in view of Lerner et al (US 5,723,598; 3/3/1998; filing date: 6/18/1996; cited in IDS) and Brenner (US 5,635,400; 6/3/1997).

D.) Claims 1, 3-10, 15 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

E.) Claims 1, 3-10, 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

F.) Claims 1, 3-10, 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using certain nucleic acids as tags for selecting certain reaction products (attached to the nucleic acid tags), does not reasonably provide enablement for using any other nucleic acid molecules to generate any chemical entities attached thereon.

New Claim Objections / Rejections

Claim Objections

6. Claims 1 and 5 are objected to because of the following informalities:

A.) The duplicated term “and” in line 5 of step (b) in Claim 1 should be deleted. In addition, the term “a” recited in front of “nucleic acid tag” in line 6 of step (f) of claim 1 should be replaced by the term “the”, because the said “nucleic acid tag” seems to be referring to the same “nucleic acid tag” recited in the preceding lines of the instant claim 1.

B.) The duplicated term “the” in line 1 of step (i) of claim 5 should be deleted.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter Rejection

8. Claims 1 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 has been substantially amended as filed on 11/19/07. However, the instant specification does not provide support for the following newly added feature, “removing said first immobilized sequence” before steps (c) and (f) of the instant claim 1. The said claim limitation does not seem to have support in the instant specification. Applicants mainly pointed

to Figure 1 and pages 6, 7, 12+ of the instant specification. However, the cited passages do not recite the “immobilized sequence” is removed from the hybridization reaction.

Claim 17 has been newly added to recite “a linker” for linking the chemical reaction site to the 5’ terminus. However, the instant specification and claims as originally filed do not appear to provide support for the said limitation.

If Applicant believes this rejection is in error, applicant must disclose where in the specification support for the entire scope of the amendment(s) and/or new claims can be found. As a result, Claims 1 and 17 represent new matter.

Second paragraph of 35 U.S.C. 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 recites the limitations “the different sequence oligomer” and “the different sequence small-molecule compound” in step (i). There are insufficient antecedent bases for these limitations in the claim. It is not clear to which “oligomer” the said first term is referring. Claim 1 from which claim 5 depends from does not recite the term “small-molecule”.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Lerner and Brenner

12. Claims 1, 3-10 and 15-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lerner et al (US 5,573,905; 11/12/1996), in view of Brenner (US 5,635,400; 6/3/1997; cited previously). This rejection is necessitated by applicant's amendments to the claims.

The instant claim recites a method of comprising: (a) providing a pool of subsets of nucleic acid tags, wherein each nucleic acid tag comprises a single stranded DNA sequence having a 5' terminus and a first variable hybridization sequence linked to a second variable hybridization sequence, wherein said 5' terminus is covalently attached to a chemical reaction site, and wherein each of said first and second variable hybridization sequences is different for each subset of nucleic acid tags;

(b) carrying out the first synthetic step by reacting the chemical reaction sites of the nucleic acid tags in each of the subsets formed in (a) with a selected one of a plurality of first reagents to convert the chemical reaction site of each subset of nucleic acid tag to a reagent-specific compound intermediate to produce subsets of reacted nucleic acid tags;

(c) pooling the subsets of reacted nucleic acid tags;

(d) forming a second group of subsets of the pooled reacted nucleic acid tags of step (c), for participation in a second synthetic reaction step, by contacting said pooled reacted nucleic acid tags with a plurality of second immobilized nucleotide sequences, each designed to capture a subset of said reacted nucleic acid tags by hybridization between one of said second hybridization sequences and the second immobilized sequence; and

(e) carrying out the second synthetic step by reacting the reagent-specific compound intermediate of the reacted nucleic acid tag in each of the subsets formed in (d) with a selected one of a plurality of second reagents."

Lerner et al, throughout the patent, teaches a method synthesizing combinatorial chemical libraries comprising various oligonucleotides and other chemical groups such as amino acids (e.g. Abstract). The reference teaches synthesis of bifunctional molecules by attaching subunits of nucleotides and amino acids to an oligonucleotide (or nucleic acids) (e.g Figure 2; col.13), which read on the “single stranded nucleic acid tags” as well as the method steps of forming the synthetic chemical reaction of **clms 1** and **23** as well as the amino acid subunit of **clms 19** and **26**.

The reference also teaches the synthesized oligonucleotides can be extended in the direction of 3' to 5' (or 5' to 3' direction) (e.g. col. 12; col.13, lines 17+), which read on the “5' terminus is covalently attached to a chemical reaction site” (as recited in step (a) of **clms 1, 18** and **25**) with the 5'-terminal nucleotide comprising the “chemical reaction site”. That is the chemical reaction of the Lerner reference is a nucleotide coupling reaction to extend the oligonucleotide at the 5' end. In addition, the terminal nucleotides in the oligonucleotides read “linkers” of **clms 17** and **24**.

The Lerner reference also teaches the oligonucleotide synthesis is conducted iteratively by repeating each synthesis step in cycles (e.g. Figure 2; Col.10+), which the steps read on the iterative synthesis of **clms 1, 5** and **23**.

The reference also teaches the synthesized oligonucleotides have various nucleic acid sequences (e.g. Figure 2; col.9, lines 48+; col.6, lines 26+), which read on the “variable” and “constant” hybridization sequences as well as the limitation “wherein each said first and second variable hybridization sequences is different from each subset of nucleic acid tags” of **clms 1** and **23** as well as the “at least 5 separate variable hybridization sequences” of **clm 6** as the term

“variable hybridization sequences” is not specifically defined in the instant specification. The reference also teaches that the oligonucleotide can be synthesized with “all combinations and permutations of an alphabet of chemical units” (e.g. col.6, lines 26+). The reference also teaches, for example, sequences within the library that share common nucleic acid sequence while possessing variable sequences (see, for example, sequences of Figure 2), which read on the limitation of **clms 7 and 29**.

The reference also teaches splitting and combining the reaction mixtures at different cycles to synthesize diverse oligonucleotides (e.g. cols 10-11), which read on the splitting and pooling steps (i.e. steps (b), (d) and (e)) of **clms 1, 5 and 23**.

The reference also teaches adding oligonucleotides (instead of single nucleotides) to the growing oligomers (e.g. col.14, lines 16+), which read on the oligomer subunits of **clm 3**. The single nucleotide reads on the “small molecule compound substituents” of **clm 4**.

The reference teaches using the synthesized oligomers or bifunctional molecules for subsequent PCR amplification and/or molecular binding interactions (e.g. cols 15+), which read on the intended uses of **clms 8 and 9**.

The reference also teaches the steps of PCR amplification, subsequent restriction digestion of the PCR product, rejoining the digested strands, etc. (e.g. Figure 1; col.3, lines 60+; col.7; col.17, lines 45+), which read on the method steps of **clm 10**. The reference also teaches enriching the libraries using the PCR/restriction products for bifunctional molecules that bind to biologically active molecules (e.g. cols.17-18, bridging), which read on the enriching steps of **clms 8, 10 and 23**.

The reference also teaches attaching the oligonucleotide onto a solid support and then conducting further oligonucleotide synthesis (e.g. col.8), which reads on the solid support attachment of **clm 16**.

The reference also teaches attaching and removal of the Fmoc protection group to the free amino acid terminus (e.g. col.5; col. 12, lines 45+), which read on the steps of **clms 20, 21, 27 and 28**.

The reference teaches oligonucleotides with regions of at least 10 nucleotides long for both the "constant" and "variable" regions (e.g. Figure 2). The reference also teaches that making chemical polymer with various lengths (e.g. col.4, lines 35+). The reference further teaches "the length of a unit identifier oligonucleotide can vary depending on the complexity of the library..." (e.g. col.6, lines 1+). Although the reference does not explicitly teach the oligonucleotides are at least 50 nucleotides long as recited in **clms 22 and 30**, it is prima facie obvious for one of ordinary skill in the art to use oligonucleotides with various sizes (such as the ones that are at least 50 nucleotides long). Thus, depending on the experimental design and the desired polymers to be synthesized (such as the needed increase in complexity of the library), a person of ordinary skill in the art would have been motivated to use oligonucleotides with appropriate lengths to generate a combinatorial library.

Lerner et al, do not explicitly teach using solid support immobilized complementary oligonucleotides for the "splitting" (or sorting) of the produced polymer molecules as recited in **clms 1, 15, 16 and 23**.

However, Brenner, throughout the patent, teaches using immobilized oligonucleotides to sort or split complementary oligonucleotides (e.g. Abstract). The reference teaches hybridizing

the oligonucleotides to a solid support through its complementary hybridization sequences (e.g. col. 12, lines 15+; Figure 4, where the solid support (245) has immobilized hybridization nucleotide sequences (250) that are complimentary to the oligonucleotide tags (255)). The reference also teaches sorting the oligonucleotides (e.g. col. 12, lines 10+). The reference teaches sorting the oligonucleotide tags into tubes, or other solid substrate (e.g. cols. 19-20).

The Brenner reference also teaches the advantages of using immobilized oligonucleotides for sorting (or splitting) their complementary oligonucleotides (through hybridization reaction) such as enabling for “automated system for manipulating and sorting polynucleotides”, and “useful in large-scale” processing (e.g. Abstract).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to use immobilized oligonucleotides to sort (or split) their complementary oligonucleotides through specific hybridization reactions.

A person of ordinary skill in the art would have been motivated at the time of the invention to use solid substrate immobilized oligonucleotides to sort their complementary oligonucleotides for various purposes, because the various advantages including automation and large-scale synthesis, as taught by Brenner et al. In addition, it would have been obvious to one of ordinary skill in the art to use the sorting method of the Brenner reference to split the polymer library of the Lerner reference. Using the known technique of oligonucleotide sorting of the Brenner reference to split oligonucleotides for combinatorial synthesis of the Lerner reference would have been obvious to one of ordinary skill.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications, because the using immobilized oligomers to sort or split oligonucleotides is routine and known in the art as taught by both Brenner et al.

Discussion and Answer to Argument

13. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants' arguments against previously set forth claim rejections over art are moot due to claim amendments and withdrawal of the previous rejections. Applicants are respectively directed to the above obviousness rejection over the Lerner (newly cited) reference in view of Brenner et al.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

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CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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1/28/08

/Jon D. Epperson/
Primary Examiner, AU 1639